

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner maintained the rejection of claims 4, 9, and
5 11-14 under 35 U.S.C. § 112, second paragraph.

Applicants have amended claim 4 as indicated above which
the applicants submit makes the objection moot.

Rejections under 35 U.S.C. § 103

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The Examiner maintained the rejection of claims 1, 5, and
10-14 under 35 U.S.C. § 103(a) as being unpatentable over
Pastan et al. (U.S. 5,635,599) in view of Lin for the reasons
or record.

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Applicants maintain the arguments previously set forth in
the amendment of 19 April 2000 (Paper No.10).

The '599 specification includes some general statements
20 that circular permutation can be applied to other "ligands"
such as antibodies, lymphokines, cytokines, receptor proteins,
hormones and growth factors. '599 also discusses a number of
general considerations for the selection of 'opening sites' in
a protein (last paragraph of column 8 through first paragraph
25 of column 9) including; that the opening site is in a region
that lacks structure; that the opening site is at a residue
that can be substituted or modified (ie. glycosylated); and
that the opening site is in a conserved region amongst a
related family of proteins, which the Examiner has relied upon
30 to establish a *prima facie* case of obviousness. The applicants
maintain the position that the Examiner has failed to
establish a *prima facie* case of obviousness. During,
prosecution the patentee ('599) refutes such general

statements by their own admission that circular permutation is unpredictable. The patentee states:

5 "Moreover, absent a showing that a particular
ligand (e.g. IL-2, IL-4, G-CSF, or GM-CSF)
retains activity when it is circularly
permuted, there is no a prior basis to expect
that a particular ligand is suitable of
circular permutation. The Examiner appears to
be in agreement with this position as she
10 states that 'claims 19, 24, 25, 30, and 31
are deemed to be free of the prior art since
no circular permuted IL-4 muteins could be
identified in the art and it would have been
unpredictable to prepare such circularly
15 permuted IL-4 muteins which retained
activity.' Prior to the present application
there was no teaching that IL-2, IL-4, G-CSF,
and GM-CSF retain their biological activity
when they are circularly permuted. Thus, the
20 prior art provides no teaching that affords
one skilled in the art a reasonable
expectation of success." (page 16 of Paper
No. 8, 07 August 1995)

It is clear that the patentee ('599) does not believe in
25 their own general statements made in the ('599) specification
about where to make opening sites in other ligands. The
patentee ('599) freely admits that without showing that a
ligand can be circularly permuted and maintains activity,
there is no basis to expect that a particular ligand is
30 suitable for circular permutation. Thus, where the prior art
(such as '599 in this case) does not indicate which parameters
are critical and does not provide direction as to which of
many possible choices is likely to be successful, the fact

that a claimed invention falls within the scope of possible combinations considered therein does not render the invention unpatentably obvious. It is respectfully submitted the Examiner has failed to prove that the prior art establishes a
5 factual basis that a circular permutein of EPO can be made and retain activity. Therefore, there is not a reasonable chance of success. The prior art merely invites further experimentation, i.e., the present rejection is based upon the repeatedly rejected improper standard of obvious to try. In
10 *re Mercier*, 185 USPQ 774 (CCPA 1975); *Ex parte Old*, 229 USPQ 196 (BPAI 1985); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *In re Geiger*, 2 USPQ2d 176 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988); *In re O'Farrell*, 7 USPQ2d 1673, 1680 (Fed. Cir.
15 1988).

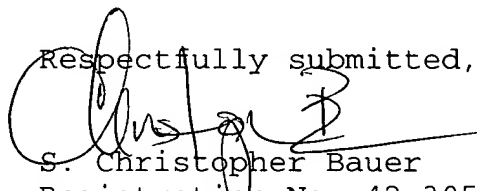
The combined teachings of these two references do not suggest the features of the present claims, and would not allow one of ordinary skill in the art to arrive at the present invention. No evidence has been presented by the
20 Examiner demonstrating a reasonable expectation of success in connection with the present invention. At most, Pastan in view of Lin would only invite one of ordinary skill to experiment with the elements disclosed therein. As pointed out above, obvious to try is an improper standard for a determination of
25 obviousness. Applicants submit that in light of these arguments that the rejection of the claims is moot.

The Examiner maintained the rejection of claims 1-4 and 6-9 under 35 U.S.C. § 103(a) as being unpatentable
30 over Pastan et al. (U.S. 5,635,599) in view of Lin and further in view of Chaudhary et al. and Cousens et al. for the reasons of record.

For the same reasons as given above Pastan and Lin do not make obvious the claimed invention. Chaudhary et al. and Cousens et al. do not remedy these deficiencies. Applicants submit that in view of these arguments the rejection of the claims is moot.

In view of the above, it is submitted that the pending claims 1-14 are in condition for allowance. Reconsideration of the rejections and objections is requested. Allowance of the pending claims at an early date is solicited. Should the Examiner find that there are unresolved issues applicants request an interview.

Respectfully submitted,



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